

REMARKS

Applicants would like to thank Examiners Epperson and Celsa for the courteous and helpful discussion held with Applicant's representative on May 28, 2003. The substance of this interview is reflected in the discussion below.

Claim Rejections - 35 U.S.C. § 112, First Paragraph – Written Description

The written description rejection of claims 1, 2, and 8 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

Applicants note that "[t]here is nothing inherently wrong with defining some part of an invention in functional terms" and that "[f]unctional language does not, in and of itself, render a claim improper (e.g., MPEP 2173.05(g), *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)). It is respectfully submitted that the claimed invention is directed to processes for preparing carriers having particular moieties (e.g., hapten molecules, marker groups, solid phase binding groups) at specific predetermined positions. The procedures for controlling the specific positions at which the moieties are introduced into the carrier are described thoroughly in the specification and are general procedures that may be used regardless of the nature of the moiety.

The use of "hapten molecules," "marker groups," "solid phase binding groups" and "reactive side groups"—that is, the functional language cited as a basis for the written description rejection—is widespread in the field of diagnostic assays and the meanings of these terms as well as numerous exemplars thereof and procedures for their use are well-established in the art (in support thereof, Applicants refer to the Exhibits A and B submitted with their Response filed July 16, 2002). In addition, all of the functional language is fully supported by and described in the specification as filed (e.g., page 7, line 33 to page 8, line 35; page 9, lines 5-8; page 9, line 26 to page 11, line 30; page 9, lines 10-16; etc.). The claimed invention is not dependent upon—and, therefore, should not be limited to—specific types of "hapten molecules," "marker groups," "solid phase binding groups" or "reactive side groups." Rather, the claimed processes for producing conjugates illustrated in the Examples may be practiced using alternative hapten molecules, markers, labeling groups, and solid phase binding groups.

In view of the preceding, Applicants respectfully submit that the specification as filed is representative of each of the independent genus claims. As such, Applicants respectfully submit that they were in possession of the claimed invention at the time of filing. For at least these reasons, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, First Paragraph – Enablement

The enablement rejection of claims 1- 8 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

Applicants note that “[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed” and that “[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation” (MPEP 2164.02).

The claimed invention is directed to processes for preparing carriers having particular moieties (e.g., hapten molecules, marker groups, solid phase binding groups) at specific predetermined positions. The specification contains both specific and general procedures setting forth how to introduce such moieties at specific positions as opposed to merely randomly or statistically, as further explained below. While the claimed invention has been enabled both with specific examples for the functionally-defined moities recited in the claims, the specification also contains direction and guidance of a general nature to enable one of ordinary skill in the art to introduce particular moieties at specific predetermined positions in the carrier without undue experimentation.

As noted above, the use of marker groups, hapten molecules, and solid phase binding groups is well known in the field of diagnostic assays. This knowledge, in combination with the specific and general teachings contained in the specification, enables one of ordinary skill in the art to practice the claimed invention beyond merely the specific representative examples provided in the specification. Accordingly, Applicants respectfully submit that there is insufficient basis for attempting to limit the

scope of the claimed invention to the specific examples in the specification, as suggested in the Final Office Action (e.g., pages 10-11).

In accordance with MPEP 2164.01(b) which states that “[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied,” Applicants respectfully submit that inasmuch as the specification does provide specific and general methods for introducing particular moieties into conjugates at specific predetermined positions, the instruction provided sufficiently correlates with the scope of the independent claims.

In accordance with MPEP 2164.08, “[h]ow a teaching is set forth, by specific example or broad terminology, is not important.” *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, 370 (CCPA 1971). With regard to the statement in the Final Office Action that “applicants have not provided any examples of “marker groups” that include “alternatives to metal chelates” (page 16, section 24), Applicants respectfully submit that the specification, in addition to describing numerous luminescent metal chelates other than ruthenium bipyridine (e.g., page 9, line 26 to page 11, line 18), also describes a variety of fluorescent labels that may be used as alternative marker groups in accordance with the present invention (e.g., page 11, lines 20-30). Moreover, Applicants respectfully point out that the use of marker groups is widespread and well-known in the art. In support of this assertion, Applicants refer to the description in the *Tam* reference cited by the Examiner (e.g., col. 10, lines 48-55), which describes fluorescent labels, radioisotope labels, and enzyme labels, and states that “[m]ethods for labeling are well known and need not be described.”

For this reason and for the reasons set forth above, Applicants respectfully submit that the claimed invention is fully enabled. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, is in part respectfully traversed and in part obviated

by amendment. As outlined below, each of the phrases identified in paragraphs A, B, C, and G on pages 17-21 and pages 22-23 of the Final Office Action has been described in the specification and/or has a well-defined meaning within the art (in support thereof, Applicants refer to Exhibits A, B, and C submitted with their Response filed July 16, 2002).

The phrase "solid phase binding groups" refers to groups that can be immobilized to a solid phase during a diagnostic assay (e.g., specification, page 9, lines 5-16). In response to the query on page 18 of the Final Office Action, Applicants hereby confirm that this phrase describes a specific interaction between a solid phase binding group and a solid phase. By way of illustration only, one example of the type of immobilization that is referred to by this phrase is embodied in the immobilization of a biotin solid phase binding group on a streptavidin-coated particle surface (e.g., specification, page 27, lines 4-8).

The phrase "predetermined positions" refers to the controlled, defined, and reproducible introduction of moieties (e.g., haptens, marker groups, solid phase binding groups) at specific positions in a carrier, which are selected in advance of introduction by an operator performing the synthesis (e.g., specification, page 6, lines 2-27; page 11, line 32 to page 14, line 24). This is quite distinct from the type of random or statistical attachment of moieties that would result if the moieties were introduced in the presence of multiple equivalent reaction sites. As an illustration of what is meant by "random or statistical attachment", it was explained during the interview that the hydroxyl group (i.e., -OH) at the C-terminus of the peptide chain in the *Tam* reference (US 5,229,490), which is mentioned in the Final Office Action (page 31), is actually part a carboxylic acid group (i.e., -COOH)—not a free alcohol—and that carboxylic acid groups generally do not appear exclusively at the C-termini of peptides. Rather, the carboxylic acid may appear elsewhere in the chain, such as in the glutamate and aspartate residues. Thus, in such a system, there would exist multiple equivalent functional groups available to react with a solid phase and, therefore, a statistical distribution of products would be expected. In other words, coupling to the carrier would take place randomly and not at predetermined positions as required by the claimed invention.

The phrase "nucleotide analogues" has been clarified in the present amendment to recite "peptidic nucleic acids."

The recitation of "protective groups" that are "selectively cleavable" is extremely well understood in the art of organic chemistry. Although the Examiner indicated a preference for the term "orthogonal" during the interview, Applicants respectfully submit that the term "orthogonal" is understood by those of ordinary skill in the art as being synonymous with the phrase "selectively cleavable." For example, the phrase "orthogonal system" is defined as "a set of completely independent classes of protective groups wherein each class of protective groups can be removed in any order and in the presence of all other classes," as evidenced by the excerpt from *Protective Groups in Organic Synthesis*, 3rd Edition attached herewith as Exhibit 1.

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 102

The rejection of claims 1-8 under 35 U.S.C. § 102(b) as being anticipated by *Crockford* has been obviated by amendment. Each of independent claims 1, 2, and 6 has been amended to recite peptidic nucleic acids and, as such, does not encompass the types of carrier molecules described in *Crockford*.

The description of carrier molecules in *Crockford* is limited to sucrose polymers (e.g., Ficoll₇₀) and bovine serum albumin (e.g., page 7, lines 25-26; claims 10, 24, 29). The Final Office Action states that "it is not clear what is encompassed by 'nucleotide analogue,'" and that "the Examiner has interpreted 'nucleotide analogue' to include sucrose polymers" (page 25, section 26). However, as noted above, the phrase "nucleotide analogue" has been clarified as "peptidic nucleic acid." *Crockford* does not teach or suggest "forming a carrier on a solid phase by linking together monomeric units ... selected from the group consisting of nucleotides, peptidic nucleic acids, and amino acids," as required by the claimed invention. Thus, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of

this reference. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 1, 3, and 5-8 under 35 U.S.C. § 102(b) as being anticipated by *Tam* is respectfully traversed. *Tam* does not teach or suggest at least one element of independent claims 1 and 8. Namely, *Tam* does not teach or suggest introducing into carriers “monomeric units covalently bound to hapten molecules and ... monomeric units covalently bound to marker groups or solid phase binding groups” (emphasis added).

In contrast, *Tam* describes multiple antigen peptide systems in which multiple antigens maybe attached to a carrier (e.g., col. 4, lines 56-60). As noted during the interview, the *Tam* reference does not teach or suggest a carrier that simultaneously contains both a peptide antigen (e.g., a hapten molecule) and a diagnostic moiety (e.g., a marker group), as required in certain embodiments of the claimed invention. Rather, when the section of *Tam* (i.e., col. 10, lines 40-55) referred to in the Final Office Action is read in its context—specifically, when read in the context of the preceding paragraph (i.e., col. 10, lines 27-34)—it is evident that the diagnostic agent described in *Tam* is intended to be used as an alternative to the peptide antigen and that the carriers described therein would not contain both a peptide antigen and a detectable marker at the same time. For example, *Tam* states that: “This invention has been described principally as it is applied to the production of vaccines based on peptide antigens. However, as will be apparent to those skilled in the art, it is not limited to such products. For example, the core molecule could be used as a carrier for ... a diagnostic agent” (col. 10, lines 27-34). Thus, the diagnostic agent described in *Tam*, which, for purposes of this argument may be compared with the marker group of the claimed invention, is cited as just one of a list of alternative entities that could be attached to the dendritic core in place of the peptide antigen. The section of *Tam* identified on page 30 of the Final Office Action (i.e., col. 10, ll. 40-55) merely provides examples of diagnostic moieties that can be used in place of the peptide antigens.

Moreover, as further noted during the above-mentioned discussion, the *Tam* reference does not teach or suggest a carrier that simultaneously contains both a

peptide antigen (e.g., a hapten molecule) and a solid phase binding group, as required in certain alternative embodiments of the claimed invention. Assuming *arguendo* that the Gly-OH residue described in *Tam* qualified as a solid phase binding group in accordance with the claimed invention, then at least one element recited in independent claims 1 and 8 would still not be satisfied—namely, that the monomeric units be introduced into the carrier “at predetermined positions.” The reasons are that the hydroxyl group (i.e., -OH) at the C-terminus of a peptide chain is part a carboxylic acid group (i.e., -COOH)—not a free alcohol—and that the carboxylic acid group does not appear exclusively at the C-terminus of a peptide. Rather, the carboxylic acid may appear elsewhere, such as in glutamate and aspartate residues. Thus, in such a system, there would exist multiple equivalent functional groups available to react with a solid phase and, therefore, a statistical distribution of products would be expected. In other words, as noted above, coupling to the carrier would take place randomly and not at predetermined positions as required by the claimed invention.

For at least these reasons, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Tam*. Accordingly, withdrawal of this ground of rejection is respectfully requested.

New Claims:

New dependent claims 9-32, all of which depend from one of independent claims 1, 2 or 8, recite specific types of hapten molecules, marker groups or solid phase binding groups that have been described in the specification. Inasmuch as independent claims 1, 2, and 8 are believed to be allowable for at least the reasons set forth above, Applicants respectfully submit that dependent claims 9-32 are likewise allowable.


Conclusion:

In view of the Amendments and Remarks set forth above, Applicants respectfully submit that the claimed invention is in condition for allowance. Early notification to such effect is earnestly solicited.

If for any reason the Examiner feels that the above Amendments and Remarks do not put the claims in condition to be allowed, and that a discussion would be helpful,

it is respectfully requested that the Examiner contact the undersigned agent directly at (312)-321-4257.

Respectfully submitted,



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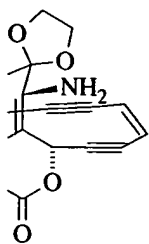


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Two new sections on included. All other sections others. The section on reflecting the trend of the natural products. An effort of protection and deprotection of alcohols as esters and attempted to be exhaustive provided that illustrate the examine some of the exceptions. The Reactivity Chart edition. The chart number when it is first introduced because of the sheer magnitude.



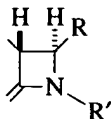
reagents and thus must be treated with pyro- by treatment with HF,

These conditions were clean conversions. yield.²⁷

ality and mildness of the igars.²⁸ The dichloroph-, but little is known of its

yield.³⁰

The phthalimide group

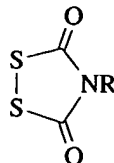


35°, 92–96% yield. The fication of oligosacchar- action.³⁴

4-Nitro-*N*-phthalimide

The 4-nitro-*N*-phthalimide, prepared by heating the amine with the anhydride to 130° for 30 min, is cleaved with MeNHCH₂CH₂NH₂ (71–92% yield). These cleavage conditions were compatible with cephalosporins, where the phthalimide was removed in 92% yield at –50° in 30 min.³⁷

N-Dithiasuccinimide (Dts–NR) (Chart 9):



Formation

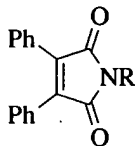
1. EtOCS₂CH₂CO₂H or EtOCS₂CSOEt; ClSCl, 0–45°, 70–90% yield.^{38–40}
2. PEG(2000)–OCS₂CH₂CONH₂; TMSNHC(O)NHTMS; ClSCl.³⁸

Cleavage

The Dts group is cleaved by treatment with a thiol and base, e.g., HOCH₂CH₂SH, Et₃N, 25°, 5 min, HSCH₂C(O)NHMe, Pyr, 5 min.⁴¹ Dithiothreitol (DIPEA, CH₂Cl₂, 87–98% yield) seems to be the most trouble-free method for Dts deprotection.^{40b} In the presence of an azide, the Dts group can be removed with NaBH₄⁴² or with HSCH₂CH₂CH₂SH (DIPEA, CH₂Cl₂, 94% yield).⁴³ The use of Zn (AcOH, Ac₂O, THF, 80–87% yield) cleaves the Dts group in the presence of the extremely sensitive pentafluorophenyl ester.^{40a}

The Dts group, stable to acidic cleavage of *t*-butyl carbamates (12 *N* HCl, AcOH, reflux; HBr, AcOH), to mild base (NaHCO₃), and to photolytic cleavage of *o*-nitrobenzyl carbamates, can be used in orthogonal schemes for protection of peptides.⁴¹ Merrifield defines an orthogonal system as a set of completely independent classes of protective groups wherein each class of protective groups can be removed in any order and in the presence of all other classes.⁴¹

N-2,3-Diphenylmaleimide:



The diphenylmaleimide is prepared from the anhydride, 33–87% yield, and cleaved by hydrazinolysis, 65–75% yield. It is stable to acid (HBr, AcOH, 48 h) and to mercuric cyanide. It is colored and easily located during chromatography, and has been prepared to protect steroidal amines and amino sugars.⁴¹